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REVIEW

Skipping a pillar does not make for strong foundations: Pharmacokinetic-pharmacodynamic reasoning behind the shape of dose–response relationships in oncology

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Abstract

Dose–response analysis is often applied to the quantification of drug-effect especially for slowly responding disease end points where a comparison is made across dose levels after a particular period of treatment. It has long been recognized that exposure – response is more appropriate than dose–response. However, trials necessarily are designed as dose–response experiments. Second, a wide range of functional forms are used to express relationships between dose and response. These considerations are also important for clinical development because pharmacokinetic (PK; and variability) plus pharmacokinetic-pharmacodynamic modeling may allow one to anticipate the shape of the dose–response curve and so the trial design. Here, we describe how the location and steepness of the dose response is determined by the PKs of the compound being tested and its exposure-response relationship in terms of potency (location), efficacy (maximum effect) and Hill coefficient (steepness). Thus, the location (50% effective dose [ED_{50}]) is dependent not only on the potency (half-maximal effective concentration) but also the compound's PKs. Similarly, the steepness of the dose response is shown to be a function of the half-life of the drug. It is also shown that the shape of relationship varies dependent on the assumed time course of the disease. This is important in the context of drug-discovery where the in vivo potencies of compounds are compared as well as when considering an analysis of summary data (for example, model-based meta-analysis) for clinical decision making.

INTRODUCTION

Dose finding via understanding dose/exposure – response relationships and optimizing dose/schedule is fundamental to the development of drugs with narrow therapeutic margins.[1] The US Food and Drug Administration's (FDA's) Project Optimus requires sponsors to explore and justify conclusions of an optimized dose/schedule in oncology. Explicit in this is the need to characterize dose/exposure response relationships for efficacy and toxicity. A dose is prescribed and so recommendations, in the absence of therapeutic drug monitoring, should be on dose. However, understanding the drug exposure required to inform this dose decision is important. When this analysis should be

done has been debated, in early studies or in late development with more mature data on efficacy.[2] Whether it is better to demonstrate efficacy before optimizing the dose/schedule, or to generate dose informative data from the first trial is still under debate. There are ethical concerns of potentially under-exposing patients with a serious life-threatening condition. In this context, there is not the concept of a "rescue therapy" that allows for lower dose levels to be fully investigated in other therapy areas.

After deciding when to do the analysis, the next question is how to do the analysis. This is generally seen as a dose–response question with the assumption that a therapeutic index exists and can be seen via a shift in the dose–response curves between efficacy and safety. This shift is important but implicit in this is an assumption that the shape of the response is the same for both toxicity and efficacy (i.e., similar slope). At the efficacy 50% of maximal effect dose (ED_{50}), there may be little toxicity but if the curve for toxicity is steep (quite often seen) then by ED_{80} for efficacy there may be increased occurrence of toxicity. Therefore, understanding all aspects of the dose–response shape is important.

Furthermore, disease and other confounding factors limit our ability to determine these relationships. More importantly, intent to treat analysis will flatten the dose–response at the top end or even appear biphasic due to toxicity and other reasons for patient dropout. Such approaches also preclude the possibility of incorporating a wide range of doses by allowing patients to be moved to a higher or lower dose level. In addition, for certain drugs (e.g., check point inhibitors) a time dependence in drug clearance is observed, thus making a link between dose and response more complex. Taking the observation time into account therefore is an important factor when choosing a dose,[3] which typical dose–response or exposure-response analyses do not consider explicitly. In addition, dose frequency is rarely considered in such analyses.

Key questions, such as: Which dose–response shape would be expected? How much statistical power is lost by a priori choosing from a range of functional forms for the dose response? These questions require a fundamental understanding of how pharmacokinetic/pharmacodynamic (PK/PD) feeds into dose response. In doing so, a library of functional forms would not need to be considered to characterize the dose–response. The modeling analysis would become hypothesis driven. Furthermore, analyses of drugs with the same or similar mechanism of action could be compared and knowledge translated forward to new compounds. Finally, an understanding of the time-course of disease[4] could be used to inform future modeling. We therefore argue that not just PKs, the first pillar of pharmacology,[5] should be considered when exploring the link between dose and efficacy but also pillars 2 and 3 (target binding and pharmacology) as well as the inclusion of disease time course as a fourth pillar.[6] Comparing drugs on total dose/concentrations is not sufficient: free drug in plasma should be used as a surrogate for free drug in tissue.

After a brief review of the current dose–response literature, we will derive dose–response models for exponential, Mayneord and Bertalanffy growth laws, to illustrate how incorporating PK/PD and disease time-course further illuminates the expected dose–response relationship. It will be shown that potency and the PK profile, including terminal half-life, not only sets the location (the ED_{50}) of the curve but also the steepness (Hill coefficient) as well.

OVERVIEW OF DOSE–RESPONSE LITERATURE

There exist numerous reviews on PK/PD and dose–response modeling.[7–11] Within the literature it appears that dose–response and exposure-response modeling have become disconnected and to some degree in practice as well. The former directly addresses labeling recommendations, however, the latter, PK/PD modeling, is an important component of identifying the optimal dose. Quantification of drug effect is an important aspect of model-informed drug discovery and development[12]: compound selection and dose selection. Dose is informed by a combination of the PK and PD properties of a drug. Therefore, for the optimal dose and frequency of dosing to be understood, these factors need to be disentangled. First, thought should be given to the question that the study and analysis will address – again, prior consideration of what the model could be and how the modeling results will be interpreted are important. A well thought out dose-(exposure) response analysis allows critical factors and covariates to be considered in the analysis.[11]

There are, of course, many complexities, especially in oncology. For example, within patient titration is an emerging strategy to improve tolerability. This has been seen with inducers of cell death, such as BCL2 inhibitors, as well as with T-cell engagers where tumor lysis and the resulting cytokine storm can be life-threatening. The opportunities for optimizing dose are demonstrated by the modeling in Stein et al. 2012[13] that led to a trial[14] investigating everolimus dose titration.

An example of the large variability in exposure at a given dose is for the drug erlotinib, where drug concentrations can span multiple orders of magnitude at the approved dose,[15] "apparent clearance estimated to 4.85 ±4.71 L/h, elimination half-life to 21.86 ±28.35

h, and apparent volume of distribution to 208 ±133 L." Given, that an exposure-response is seen in certain disease settings,[16] erlotinib would therefore benefit from a therapeutic drug monitoring[17] approach. This example demonstrates how seeing a dose–response for the drug is likely to be very difficult. Typical phase II and III study designs in oncology usually use no more than two dose levels, which can potentially limit the ability to identify a dose- (or exposure) response relationship using these modeling tools.

The dose-response literature reviews exhibit a wide range of models, quadratic, linear, exponential, and maximum effect (E_{max}). One first asks: Aren't they just parts of the same global curve? MCP-MOD[18] is an example of considering a library of functional forms and calculating contrasts to test for the presence of a dose response. This is a rational approach, however, there can be a subsequent loss of power due to the need to test multiple hypotheses (https://www.fda.gov/media/99313/download). Second, the assessment and optimization require a dose response for toxicity to be derived – bringing in an even greater number of choices. Thus, it would be preferable to understand the underlying PK/PD behind a potential dose-response relationship.[19] The PK half-life, and its resulting impact on PD half-life[20] should be considered in the optimization of dose and schedule as well. These will inform on the likely accumulation of drug and effect over time[21] after repeated administrations of drug which will influence the dose-response relationship.

Typically, dose–response modeling considers a sigmoidal-shaped curve[22] – or linear in the absence of saturation of effect. This curve shape has its origin in the Langmire binding isotherm with further formalization with the development of the operational model of agonism[23] and the effects of antagonists on this system. However, these are effects right at the beginning of the pharmacological causal chain, so why would the dose-response curve for efficacy, pillar 4 phenotypic changes, be expected to follow this trend as well? The only justification is that it models a bounded response with the curve plateauing asymptotically to a maximum effect – which is often observed.

However, one important consideration is that these generic curves do not consider time – whereas trials will generate time-dependent information. It is often the case that trial participants are not all assessed at the same time after the start of treatment. The apparent potency of a drug, if dose versus effect is plotted, is time-dependent when there is a delay in the observed onset of drug action – the true underlying potency will remain unaltered. This might be due to slow distribution of drug into tumor, or slow "off rate" binding kinetics, however, these tend to operate on the order of minutes to hours. The third reason for a PK/PD time delay is due to the slow turnover of the biomarker – in this case, the tumor burden in the patient or mouse model. Those processes are operating on the order of weeks and so careful choice of the PK metric to compare to efficacy end points is important. Time series analysis should be performed when the system is not considered to be at steady-state – important for early induction phase as well for intermittently dosed treatments. The effect of time will be considered in further detail below.

There are many clinical modeling studies that include the analysis of time series of tumor burden. Unfortunately, very few of these contain a true dose-response element – at least a dose range wide enough that dose dependency can be determined above a pairwise comparison. The power of bringing in time components was illustrated by Dickinson et al.[24] where a single time series model is applied that significantly improves the precision of analysis, and so the power. There have been few attempts to bring time-dependent effects on slow biomarkers into classic exposure response analyses[25] but these tend to be very empirical and "area under the curve (AUC) driven." Other examples of exposure response modeling approaches are available that do consider disease burden time series.[26]

CONSIDERATIONS FOR MODELING DOSE RESPONSE

There are some key principles that should be considered to ensure the modeling analysis will deliver what is expected. Modeling need not be complex, but it should reflect the key aspects of the biology, pharmacology, and experimental design. The following is generally obvious, however, many of the steps of model development are often implicit. Prior information, assumption-setting, and validation[12] are all important steps in model development. It is useful to take a step back and consider from first principles what is likely to be observed. The following section discusses key aspects that should be considered.

First, we must define the question we wish to answer, and this will define what we wish to estimate from the data and therefore the end points and the analytical approach. The estimand will likely be the parameter values that provide the best model description of the data. However, what we wish to estimate might be derived from the model (e.g., the dose level that gives 90% of the maximum effect or whether there is an efficacy advantage to twice daily versus once daily dosing). Second, the analytical approach should then be translated mathematically to a model that will enable estimation of these key parameters – perhaps taking care to parameterize

the model directly with the required estimands – for example, parameterize in terms of dose or concentration for 90% effect rather than derive from 50% effect level (ED_{50} or EC_{50}) and the Hill slope. We shall show below how careful analysis at this step can reveal the data trends the model implicitly predicts. Consideration should be made of the statistical aspect of the model especially with reference to sources and levels of variability and potential covariates. Finally, this structural and statistical model are combined via computer coding and applied to the data.

Biological considerations

First, the nature of the disease in terms of its typical rate of progression and evolution needs to be accounted for. As discussed above, the effect observed is dependent on the time at which observations are made. Cancer is a complex disease with many contributing factors to the observed phenotype[27] – including the rate at which tumors grow and metastasize. However, in all cases, trials record some measure of disease burden, tumor size, and Response Evaluation Criteria in Solid Tumors. Thus, consideration of the appropriate model structure for modeling disease progression[4,28] is required to correctly identify the PK/PD relationship and ensure the model is predictive. This will allow alternate dosing regimen to be considered prospectively. An important process to take into consideration is resistance.[29] The source of resistance (or at least whether it is pre-existing or emergent under treatment), whether it is reversible, and what impact it will have on the pharmacology of the drug –an alteration of E_{max} or potency (EC_{50}) over time – should be considered.

The second biological consideration is the relevant end point(s) to incorporate into the model. There are many end points (PKs, tumor size, progression-free survival, disease control, and overall survival [OS]) that are measured in a clinical trial and the challenge is to choose those most relevant to the questions in hand. In many cases, there is not a direct target engagement biomarker. For example, kinase inhibitors where we can measure phosphorylation of substrate. The effects of DNA damage response inhibitors or checkpoint inhibitors can only be measured several steps down stream. This potentially limits our ability to quantify how well the mechanism is being tested and feed into dose optimization. Typically, tumor volume changes are considered for modeling. However, no publications exist that show across a wide range of randomized clinical trials with an OS difference that the metrics from such modeling endeavors fully capture the treatment effect observed on OS and satisfies the Prentice criteria[30] for surrogate end points. Thus, can tumor response still be used as an early pharmacological biomarker to optimize dose? It certainly is the most accessible and data rich with time dependency that might allow dose and schedule dependence to be investigated.

Pharmacological considerations

Considering the causal chain of pharmacology, with the pillars imbedded in it, it is clear that PKs, mode of binding, and mechanism of action should be taken into account when characterizing the dose–response.

PKs is a key consideration because this is the link between dose and the extent and duration of exposure of the body to the drug. If we are to incorporate a PK/PD relationship, then we must know what free drug concentrations are achieved in plasma and relevant tissues. The route of administration, and bioavailability, as well as the rate and extent of distribution[31] will inform on this as will the clearance of the drug. Together these will predict the extent (maximum plasma concentration, AUC, trough plasma concentration) and duration (half-life) of the drug exposure. We will see these are key parameters in the dose-response relationships that we will derive below.

Second, the binding characteristics and the anticipated pharmacology will inform the relationship between dose and effect. Is this an orthosteric or allosteric inhibitor? Is binding reversible or irreversible – and, if irreversible, what is the re-synthesis rate of the target protein? The answers to these questions will provide insight into target occupancy over time. Moving to the third pillar: what is the mechanism? What is the cancer hallmark being targeted and how is the target involved in this process? How rapidly is this likely to respond? The answer to these questions will inform on how target occupancy is translated to effect and thus completing knowledge of the PK/PD relationship. Where is the location (EC_{50}) of this relationship? Is it likely to be a standard sigmoid or steep? Finally, is this a combination with another agent – either experimental or current standard of care? What is its mechanism of action? What is the hypothesized pharmacological interaction of these two treatments?

A priori knowledge, perhaps in the form of preclinical studies, including quantitative target validation, combined with early clinical PK and biomarker data, should begin to answer the above questions. Other modalities – for example, T-cell engagers, PROTACs with potentially biphasic concentration effect relationships, and ADCs with DAR dependencies (dose of ADC vs.

payload) may appear more complex but will have similar considerations.

Study design considerations

The key design aspects to consider are the dose levels, frequency, and duration of dosing. Coupled with the time, or times, of end point assessment allows the proposed model to be simulated and therefore parameter estimation to be performed. There are other factors in the design that require consideration.

Is a dose titration planned and how will this be conducted? Will patients be able to move to another dose level/treatment group and how will this decision be made? Will this and any other adaptions or dropouts introduce bias – and how will this be handled in the analysis? Recent publications[32,33] have carried out simulation studies and have found that these can be accounted for if underlying covariate effects are included.

Finally, potential sources of variability and important baseline covariates should be carefully considered to make the analysis as broad as possible and so account for confounding effects. This is important for a major source of confounding: the impact of the disease on PKs and PDs.[34] This clearly merits more than one dose level being explored so these can potentially be separated[7] along with baseline covariates that will enable the disentangling of these relationships.

INTERACTION BETWEEN THE DISEASE PROGRESSION MODELS AND HOW THE PK/PD RELATIONSHIP DETERMINES THE SHAPE OF THE DOSE–RESPONSE RELATIONSHIP

We will now consider a series of case studies of commonly used tumor growth laws and show how the considerations of time scale of disease, incorporation of the pharmacology of the treatment, and time of end point assessment result in a particular shaped dose–response curve. These derivations will include an expression for the AUC[35] that is useful in contexts outside of oncology. Full derivations are given in Appendix S1. The utility of this modeling exercise is not just to illustrate how we might anticipate the shape of the dose–response curve, and so aid planning of studies, such as anticipating the required dose range and time(s) for end point assessment. These might also find application as K-PD[36] models using a theoretical one-compartment model to drive a disease progression "PD" model.

Case study: Exponential growth

Consider an exponential growth process with a drug-effect that reduces the rate of growth or, if the E_{max} is sufficiently large, can reduce the size of the population:

$$\frac{dV}{dt} = V\left(k - E_{\max}.\frac{C(t)}{(EC_{50} + C(t))}\right)$$

where V is the tumor volume, k is the growth rate, and EC_{50} is the drug concentration for 50% of maximal effect. The initial condition is:

$$V(0) = V_0$$

and the dose-dependent (D) PKs are described using a one-compartment i.v. bolus dose model in terms of clearance (CL), and volume of distribution (V_d):

$$C(t) = \frac{D}{V_d}e^{-at},$$

where the elimination rate constant $a = \frac{CL}{V_d}$.

The solution to this ordinary differential equation (ODE) is

$$V(t) = V_0 e^{kt}\left(\frac{EC_{50} + \left(\frac{D}{V_d}\right)e^{-at}}{EC_{50} + \left(\frac{D}{V_d}\right)}\right)^{\frac{E_{\max}}{a}}$$

a similar result has been reported before.[37] For long time (for $t >> 1/a$):

$$V(t) = V_0 e^{kt}\left(\frac{EC_{50}}{EC_{50} + \frac{D}{V_d}}\right)^{\frac{E_{\max}}{a}}$$

Thus, for long time, a standard sigmoidal dose–response curve is predicted whose steepness is defined by the ratio of the maximum rate of effect and the washout rate of the drug (see Figure 1). The steepness as determined by the PK half-life is due to the increasing time over EC_{50} with increasing doses. If a compound has a short half-life (large a), then an incremental increase in dose will result in incremental increases in the time above EC_{50}. Conversely, for a compound with a long half-life (small a) the compound will go from being below EC_{50} for the entire dosing period to exceeding EC_{50} for the entire dosing period over a relatively narrow dose range – thus resulting in a steeper dose response.

Notice also that the ED_{50}, in this case is $(EC_{50}V)^{a/E_{max}}$, so that not only potency and PKs but the E_{max} determines the location of the curve on the dose axis. In the case of oncology, the sigmoidal relationship represents the apparent

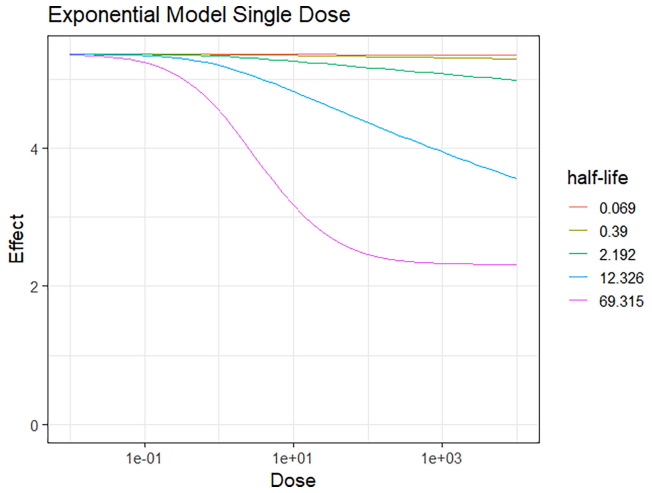

FIGURE 1 Dose response plots for the exponential growth model. *Y* axis effect is tumor volume. $E_{max} < k$ so drug can only slow tumor growth. $V(0) = 1$. Dose–response after 14 days left shifts as PK half-life increases. Parameters (CL, V_d, V_0, k, E_{max}, and EC_{50}) = (0.01–10, 1, 1, 0.005, 0.0025, and 1) units of days and liters. CL, clearance; EC_{50}, half-maximal effective concentration; E_{max}, maximum effect; k, growth rate; PK, pharmacokinetic; V_d, volume of distribution; V_0, initial tumor volume.

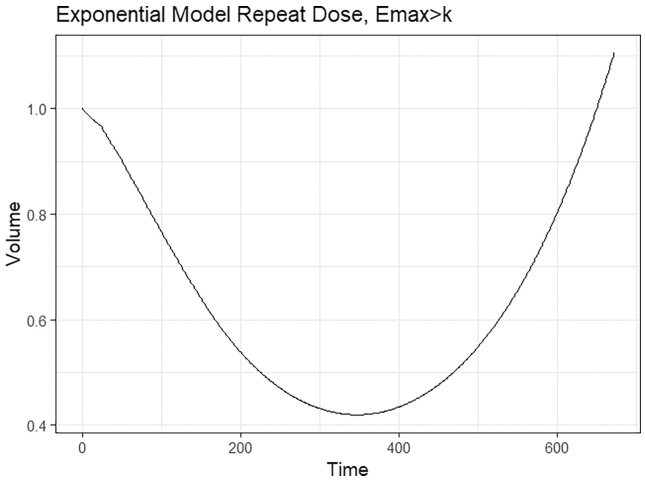

FIGURE 2 Time versus volume plot for the case of repeat dosing with the exponential model. Parameters (CL, V_d, V_0, k, E_{max}, and EC_{50}) = (0.01, 1, 1, 0.005, 0.01, and 1), units of days and liters. CL, clearance; EC_{50}, half-maximal effective concentration; E_{max}, maximum effect; k, growth rate; V_d, volume of distribution; V_0, xxx.

fraction of tumor left viable after treatment. At first sight, the above equation implies it is possible to shrink the tumor even if E_{max} less than k, however, recall the above

$$\frac{E_{max}}{a}\ln\left(\frac{EC_{50}+\frac{D}{V_d}}{EC_{50}}\right)\approx\frac{E_{max}}{a}\ln\left(1+\frac{D}{V_d EC_{50}}\right)\approx\frac{E_{max}}{a}\frac{D}{V_d EC_{50}}=\frac{E_{max}}{EC_{50}}\frac{D}{CL}=\frac{E_{max}}{EC_{50}}AUC$$

is a long-time approximation and so an untreated tumor will have grown over this period. Figure 1 confirms this for where E_{max} less than k: at high doses the effect plateaus short of tumor shrinkage. Notice that for single timepoint measurement we cannot disentangle E_{max} from the drug half-life. Figure 2 shows an example simulation where E_{max} greater than k and so tumor shrinkage can occur.

Notice for this single dose case the time of the tumor volume nadir is:

$$t = -\frac{1}{a}\ln\left(\frac{k.EC_{50}.V_d}{D(E_{max}-k)}\right)$$

which shows a logarithmic relationship with dose. This solution is only real in the case that $D > \frac{EC_{50}.V_d}{\frac{E_{max}}{k}-1}$. Substituting into the time solution for tumor volume we obtain

$$\frac{V_{nadir}}{V_0}=\left(\left(\frac{E_{max}}{k}-1\right)^k\left(\frac{E_{max}}{E_{max}-k}\right)^{E_{max}}\left(\frac{\left(\frac{D}{EC_{50}V_d}\right)^{\frac{k}{E_{max}}}}{1+\frac{D}{EC_{50}V_d}}\right)^{E_{max}}\right)^{\frac{1}{a}}.$$

Thus, an apparent sigmoidal relationship would appear for the best overall response.

The observation of "AUC driven" effect is explained by the case where over the dose range considered EC_{50} greater than D/V. Thus, by taking the Taylor series of the natural logarithm:

and substituting back into the ODE solution, an exponential-dose effect is observed that correlates with AUC:

$$V(t) = V_0 e^{kt-\frac{E_{max}}{a}AUC}$$

It can be shown similarly that if the PK/PD relationship is steep with Hill coefficient n:

$$\frac{dV}{dt} = V\left(k - E_{max}.\frac{C(t)^n}{\left(EC_{50}^n + C(t)^n\right)}\right)$$

then this relationship becomes

$$V(t) = V_0 e^{kt}\left(\frac{EC_{50}^n+\left(\frac{D}{V_d}\right)^n e^{-ant}}{EC_{50}^n+\left(\frac{D}{V_d}\right)^n}\right)^{\frac{E_{max}}{an}}$$

with similar asymptotic properties.

Note that a steeper PK/PD relationship results in a potentially less steep dose response – because duration

of near maximal effect is not as readily obtained even for longer half-life drugs: the PK half-life has taken on a "PD half-life" due to the steepness of the PK/PD relationship.

Now consider regular repeat dosing so that long-term treatment effects can be modeled and the consequences of drug accumulation on this effect, including where dose fractionation is considered. We assume that a drug is dosed at a fixed dose level D every τ hours. For q.d. dosing $\tau = 24$ h, for b.d. dosing $\tau = 12$ h. The PK profile after N doses is described as:

$$C(t) = \frac{D}{V_d}\Sigma_{i=0}^{N-1} e^{-a(t-i\tau)}$$

The solution (see Figure 2 for a time series plot), for long time, to this is:

$$V(t) = V_0 e^{kt}\left(\frac{EC_{50}}{EC_{50} + \frac{D}{V_d}\frac{1}{1-e^{-a\tau}}}\right)^{\frac{E_{max}N}{a}}$$

Notice that the effect of per dose administration is

$$\left(\frac{EC_{50}}{EC_{50} + \frac{D}{V_d}\frac{1}{1-e^{-a\tau}}}\right)^{\frac{E_{max}}{a}}$$

Thus, going from acute to chronic treatment there will be an apparent reduction in the ED_{50} by (approximately) the accumulation factor $1 - e^{-a\tau}$. Figure 3 shows a comparison of the dose-response relationship for single and repeated daily administration as a function of drug half-life.

The impact of dose fractionation

With this mathematical frame-work dose and schedule are not two separate factors, therefore they can be integrated into a single, mechanistic curve. Consider a dose fractionation study comparing q.d. (N doses) versus b.d. (2N doses) dosing. Then, from a total daily dosing perspective, the predicted long-term effects will be:

$$E_{q.d.} = \left(\frac{EC_{50}}{EC_{50} + \frac{D}{V_d}\frac{1}{1-e^{-24.a}}}\right)^{\frac{E_{max}N}{a}}$$

$$E_{b.d.} = \left(\frac{EC_{50}}{EC_{50} + \frac{D}{2V_d}\frac{1}{1-e^{-12.a}}}\right)^{\frac{E_{max}2N}{a}}$$

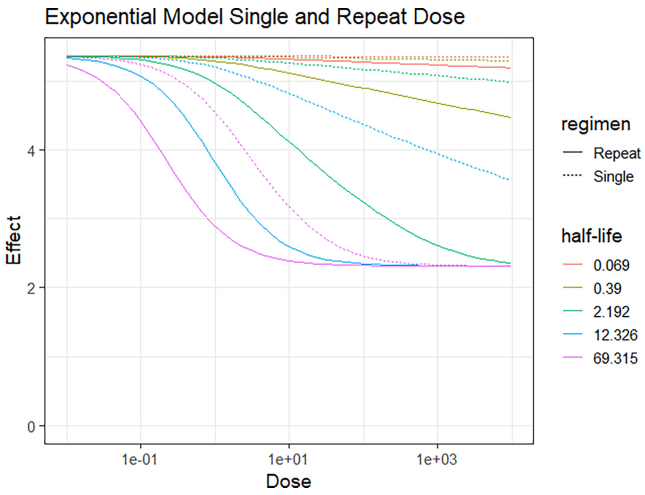

FIGURE 3 Single dose compared to repeat dose (14 days, tumor volume measured on final day) for the exponential model. Parameters (CL, V_d, V_0, k, E_{max}, and EC_{50}) = (0.01–10, 1, 1, 0.005, 0.0025, and 1) units of days and liters. CL, clearance; EC_{50}, half-maximal effective concentration; E_{max}, maximum effect; k, growth rate; V_d, volume of distribution; V_0, xxx.

Thus, b.d. would be more effective if

$$\left(\frac{EC_{50}}{EC_{50} + \frac{D}{V_d}\frac{1}{1-e^{-24.a}}}\right) > \left(\frac{EC_{50}}{EC_{50} + \frac{D}{2V_d}\frac{1}{1-e^{-12.a}}}\right)^2$$

This holds if

$$\frac{AF_{q.d.} - AF_{b.d.}}{AF_{b.d.}^2} < \frac{D}{V_d EC_{50}}$$

where

$$AF_{q.d.} = \frac{1}{1-e^{-24a}}$$

$$AF_{b.d.} = \frac{1}{1-e^{-12a}}$$

Which is always true, however the gains may be marginal as shown below especially for long half-life drugs (see Figure 4).

Case study 2 of sub-exponential processes: Mayneord's model of linear radial growth

What if the disease progression is not exponential? We consider sub-exponential growth models that are used in oncology. The Mayneord growth law[38] is defined as:

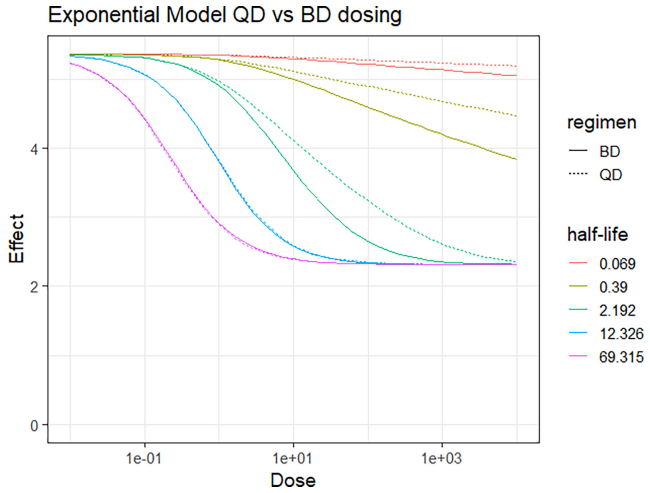

FIGURE 4 Q.d. versus b.d. dosing where "Dose" is the daily dose (e.g., 10 q.d. vs. 5 b.d.) for the exponential model. Parameters (CL, V_d, V_0, k, E_{max}, and EC_{50}) = (0.01–10, 1, 1, 0.005, 0.0025, and 1) units of days and liters. CL, clearance; EC_{50}, half-maximal effective concentration; E_{max}, maximum effect; k, growth rate; V_d, volume of distribution; V_0, xxx.

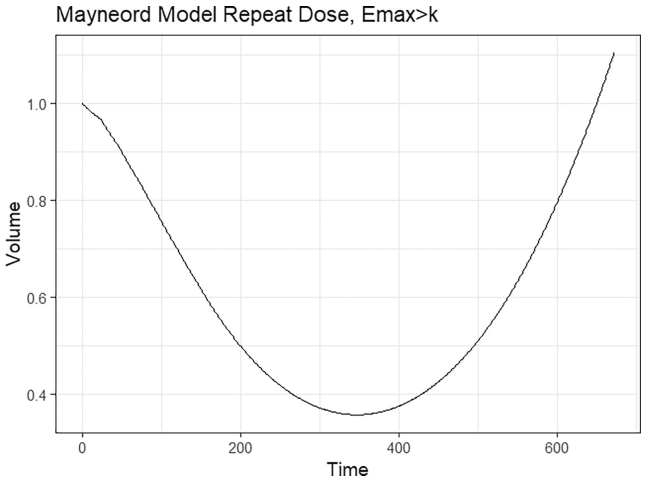

FIGURE 5 Time versus volume simulation for the case of repeat dosing for the Mayneord model. Parameters (CL, V_d, V_0, k, E_{max}, and EC_{50}) = (0.01–10, 1, 1, 0.005, 0.01, and 1) units of days and liters. CL, clearance; EC_{50}, half-maximal effective concentration; E_{max}, maximum effect; k, growth rate; V_d, volume of distribution; V_0, xxx.

$$\frac{dV}{dt} = kV^{2/3}$$

This has the solution:

$$V(T) = \left(\frac{k}{3}T + V_0^{1/3}\right)^3.$$

We can also incorporate a PK/PD effect in the model:

$$\frac{dV}{dt} = V^{2/3}\left(k - E_{max}\frac{C(t)}{(EC_{50} + C(t))}\right)$$

Notice here that $[E_{max}] = L.T^{-1}$. With the PK model $c(t)$ defined as before the dose response is

$$V(T) = \left(\frac{k}{3}T + V_0^{1/3} - \frac{E_{max}}{3a}\ln\left(\frac{EC_{50} + \frac{D}{V_d}}{EC_{50} + \frac{D}{V_d}e^{-aT}}\right)\right)^3$$

Note that $[E_{max}/a] = [L]$ and so the effect is the reduction of tumor radius over time. Note also, at larger time, the drug effect is $\frac{E_{max}}{3a}\ln\left(1 + \frac{D}{V_d EC_{50}}\right)$, and so a log-linear dose effect (similar but not identical to a sigmoid) would be observed.

Similarly, a repeat dose relationship (over N doses τ time apart) is:

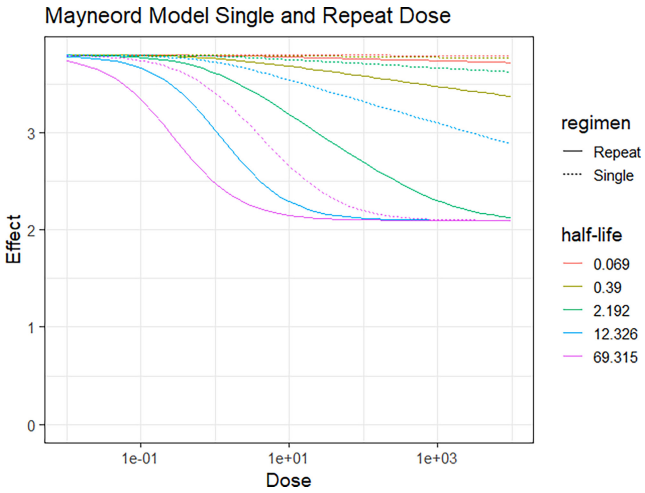

FIGURE 6 Single versus Repeat dose plot for the Mayneord model. Parameters (CL, V_d, V_0, k, E_{max}, and EC_{50}) = (0.01–10, 1, 1, 0.005, 0.0025, and 1) units of days and liters. CL, clearance; EC_{50}, half-maximal effective concentration; E_{max}, maximum effect; k, growth rate; V_d, volume of distribution; V_0, xxx.

$$V(T) = \left(\frac{k}{3}T + V_0^{1/3} - \frac{E_{max}}{3a}\Sigma_{i=1}^{N}\ln\left[\frac{EC_{50} + \frac{D}{V_d}\left(\frac{1-e^{-ai\tau}}{1-e^{-a\tau}}\right)}{EC_{50} + \frac{D}{V_d}e^{-a\tau}\left(\frac{1-e^{-ai\tau}}{1-e^{-a\tau}}\right)}\right]\right)^3$$

Figure 5 shows a time series plot for this solution and Figure 6 has a comparison of single and repeat dose–response relationships as a function of drug half-life.

Case study 3 of sub-exponential processes: Bertalanffy

As a final example, we examine the Bertalanffy model because this model allows for sub-exponential growth, like the Mayneord model, but also has an explicit cell death k_d, that allows for the tumor size to plateau.

The governing equation for the Bertalanffy model

$$\frac{dV}{dT} = kV^{2/3} - k_d V$$

The solution to which is:

$$V(t) = \left(\frac{k}{k_d} + \left(V_0^{\frac{1}{3}} - \frac{k}{k_d}\right)e^{-\frac{k_d}{3}t}\right)^3$$

We consider the case where the drug effect is to slow cell proliferation.

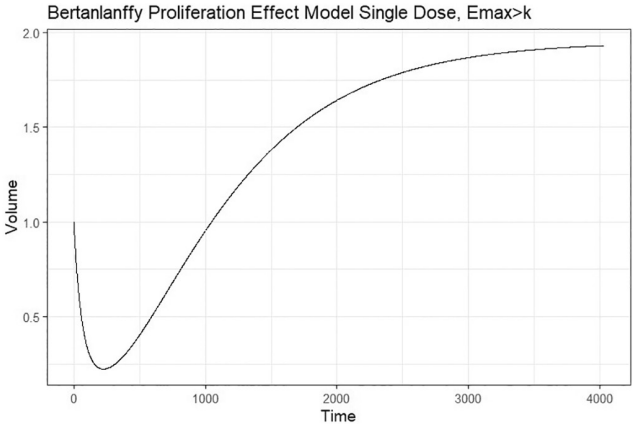

FIGURE 7 Time dependent response of Bertalanffy model after a single dose of drug. Parameters (CL, V_d, V_0, k, k_d, E_{max}, and EC_{50}) = (0.01, 1, 1, 0.005, 0.004, 0.01, and 1) units of days and liters. CL, clearance; EC_{50}, half-maximal effective concentration; E_{max}, maximum effect; k, growth rate; V_d, volume of distribution; V_0, xxx.

Bertalanffy with a drug-dependent reduction in proliferation rate

We consider the case is where the drug effect is applied to the proliferation component of the model:

$$\frac{dV}{dT} = \left(k - \frac{E_{max}C(t)}{EC_{50} + C(t)}\right)V^{2/3} - k_d V$$

In this case, the solution is:

$$V(t) = \left(\frac{k}{k_d} + \left(V_0^{\frac{1}{3}} - \frac{k}{k_d} - \frac{E_{max}}{3a}\Sigma_{n=0}^{n=\infty}\frac{(-1)^n}{n - \frac{k_d}{3a} + 1}\left(\frac{D}{EC_{50}V_d}\right)^{n+1}\left(1 - e^{-a\left(n - \frac{k_d}{3a} + 1\right)t}\right)\right)e^{-\frac{k_d}{3}t}\right)^3$$

The infinite polynomial series is similar to that of the Taylor expansion for $\ln(1+x)$ and so a relationship similar to a log linear effect of dose emerges. Its similarity is dependent on the size of $k_d/3a$. Unfortunately, due to its derivation, the above solution is only applicable for $(D/EC_{50}V_d)$ less than 1. A plot of the time behavior of this model is shown in Figure 7.

Expressions for the response of the Bertalanffy model after repeated dosing can be derived with a similar logic to the exponential and Mayneord models – however, the resulting expressions will be significantly more complex.

DISCUSSION

This review has highlighted the need to use models to explore scenarios and so generate hypotheses on optimal dose and schedule, as well as experimental design. The modeling need not be complex, but should reflect the key aspects of the biology, pharmacology, and experimental design to ensure the inference is relevant. In developing such a model, biological and pharmacological priors in the analyses can be included. In addition, simplicity allows for the more robust application of nonlinear mixed-effects in the analysis. Taking a step back and considering from first principles what we would expect to observe is important. The analysis, incorporating pillars of pharmacology (PK, PD, and disease progression) has shown that the shape of the dose–response relationship is dependent upon the underlying disease progression dynamics, the times of end point assessment, and the mechanism informed PK/PD relationship. The simulations in the figures demonstrate that the range of dose levels, dosing frequencies, and times for end point assessment can be selected with consideration to prior mechanistic knowledge. Therefore, a consideration of all the pillars of pharmacology will provide a strong foundation for trial design and interpretation by anticipating the dose and time dependence of response.

Historically there has been a gulf between very empirical PK/PD modeling and mechanistic insight. Is this gulf the driver behind the interest in Quantitative Systems Pharmacology modeling? The authors believe that these approaches are part of a modeling continuum, and it

should be the case that the appropriate (modeling) tool is used for the job in hand: therefore, could these approaches meet somewhere in the middle?

The analyses highlight explicitly that the location and the shape of the dose-response relationship is dependent not only on the potency and other pharmacological considerations but also the pharmacokinetics of the drug. This observation is to be naturally expected, however, it is worth making this explicit:

1. Dose response can change across different populations due to PK changes – terminal half-life as well as potency differences.
2. Dose response can change across species due to differences in PKs – this has implications for the extrapolation of doses tested in pivotal toxicology studies to human starting and maximally safe doses. PK/PD plus predictions of human PK is a much more sensible approach.
3. Dose response can alter dependent upon the time of endpoint assessment and whether this varies between trial participants.

The analyses do omit two important concepts in oncology. Namely drug resistance and the combination of drugs to counter this. In a very simple manner, resistance can be factored into the above models by including a time-dependent reduction in potency (EC_{50}) or efficacy (E_{max}) in the repeated dose case. Which of these is most appropriate is dependent upon the mechanism – whether it is an adaption of the whole cell population (EC_{50}) or emergence of completely resistant clones (E_{max}). Combinations might require solving the ODEs directly to incorporate the different PK and PD properties of the treatments. However, as a simple comparison of, for example, standard of care versus standard of care plus novel therapeutic, a consideration as to whether the combination alters potency or E_{max} would enable the above derivations to be used.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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